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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/103,745 | 06/24/1998 | SUDHIR AGRAWAL | 475.08.642CI | 3401 |

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| EXAMINER |
|---|
| SCHULTZ, JAMES |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 26 |

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Ex 6

| Office Action Summary | Application No. 09/103,745 | Applicant(s) AGRAWAL, SUDHIR | |
|---|---|---|---|
| | Examin r J. Douglas Schultz | Art Unit 1635 | |

*-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

1. Applicant's response filed April 30, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed November 19, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Arguments*

Claims 1, 3 and 4 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,856,462 for the same reasons of record cited in the Office action mailed September 9, 1999. It is acknowledged that Applicant's response to the double patenting rejection of Sept. 9, 1999 indicated that, should any pending claims be indicated as allowable, applicant will file a Terminal Disclaimer disclaiming the portion of the term of the patent beyond the expiration date of U.S. Patent Number 5,856,462.

3. Claim 1 stands rejected under 35 U.S.C. 102(a) as being anticipated by either of Krieg et al. (WO/9602555A1) or Krieg et al. (Antisense or Nucleic Acid Drug Development), for the same reasons of record as set forth in the Office action of September 9, 1999.

Applicants argue that the reference of Krieg et al. (WO 96/02555; Krieg I) does not anticipate applicant's claimed invention, because claim 1 has been amended to remove subject matter pertaining to methylcytosine CpG that caused said claim to read on the prior art. However, this was not the cited reason that Krieg I is considered to anticipate applicants claimed invention. Applicants' broad language recite an "inverted" CpG (i.e. a GpC motif) encompasses any motif containing a GpC, which is taught by Krieg I as shown below. Applicants' claim 1 requires an oligo possessing the following limitations: A) a modified CpG motif that is selected from one of the following-- alkylphosphonate, 2'-substituted, stereospecific phosphorothioate, phosphotriester, inverted (GpC), phosphoroamidate, or 2'-5' CpG, B) phosphorothioate linkages, and C) that it is complementary to a gene for which inhibition of expression is desired. Krieg I teaches A) an immunoinhibitory oligonucleotide comprising a 5'GCGXnGCG3' motif (page 8, line 31) which contains an "inverted" (i.e. GpC) dinucleotide motif that meets the definition of "inverted" on page 11 line 4 of applicants' specification, B) that such immunoinhibitory oligos are stabilized with phosphorothioate linkages (on page 8 line 39), and C) that these oligos can be part of antisense compounds that can be used to inhibit the expression of a gene of interest. Thus, despite applicants' arguments, the claims as written are still sufficiently broad to encompass the cited prior art.

Applicants argue that the inverted CpG taught by Krieg et al. is "fortuitous", and that applicants inverted CpG is somehow distinct from that of Krieg. However, beyond this assertion,

applicants have failed to point out how or why applicants oligos are patentably distinct. Should applicants feel that there is a structural distinction in the instant claim 1 that is not addressed by Krieg I, applicants are invited to point out with particularity by page and line number where such a difference exists. As written, the structure of the instant claim 1 and that of the prior art appear identical. As per M.P.E.P.

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Furthermore applicants arguments that Krieg et al. "predominantly" teaches immunomodulatory oligonucleotides that do not involve antisense effects is not considered relevant, because Krieg et al., no matter how underemphasized applicants believe Krieg I's teaching of antisense is, nevertheless teach all the elements of the claim above. Applicants' assertion that Krieg's "passing reference" to antisense oligonucleotides does not constitute sufficient grounds to reject the instant claim because Krieg et al. teaches that a preferred embodiment is a 5'methyl CpG not claimed by applicant is not convincing, because the issue of methylation is not an element of the instant claim. Regardless of whether the oligo of Krieg et al. is methylated, the reference of Krieg et al. teaches all the elements of applicants claimed invention. The rejection is therefore maintained.

Regarding applicants arguments that Krieg et al. (Antisense and Nucleic Acid Drug Development, 6:133-139, Krieg II) does not teach an antisense oligo that comprises both a phosphorothioate linkage and an inverted CpG motif, applicant is pointed to the methods section, left column, last paragraph bridging to next page, where a discussion of phosphorothioate substituted oligos and the sequences that contain them is held. Clearly, phosphorothioate

oligonucleotides are made, used, and discussed throughout this reference. Furthermore, several of the disclosed oligos at the top right column of page 134 contain inverted CpG (i.e. a GpC dinucleotide as defined by applicants specification on page 11). Contrary to applicants assertion, simply because Krieg II discusses other types of backbone modifications in addition to phosphorothioate modifications does not dilute Krieg's teaching directed to an oligo containing a phosphorothioate linkage and an inverted CpG motif. For these reasons, this rejection is maintained.

Claims 3 and 4, stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using the contemplated compounds in cell culture, does not reasonably provide enablement for methods of treating mammals or methods of therapy using the instantly contemplated compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the Office action of September 9, 1999. Furthermore, new claim 5 is rejected for the same reasons as claims 3 and 4; response to Applicant's arguments and elaboration on the reasons for lack of enablement are outlined below.

Applicants have argued that the specification as filed does provide *in vivo* data that supports the claims directed to methods of modulating gene expression in a mammal or to methods of treating a disease comprising administering phosphorothioate antisense oligos containing modified CpG's. Applicant cites a passage from Agrawal, cited by the examiner in a previous Office action, in stating that there are many examples in the prior art citing greater sequence specific antisense activity in *in vivo* models than in *in vitro* models.

This is not considered convincing. Applicants' claims are directed to antisense-mediated gene inhibition using the antisense oligos of claim 1, while none of the *in vivo* data provided shows antisense-mediated gene inhibition, which was the basis of the instant enablement rejection. While the data do disclose a reduction of the levels of liver enzymes ALT and AST, these enzymes are considered to reflect liver function, and their reduction is considered to result from a reduced immune response, not from antisense-mediated gene inhibition due to antisense targeting of said enzyme expression. In other words, said liver enzymes were not disclosed by applicants as being targeted for inhibition by the claimed antisense oligos. Therefore, such data is not considered to be relevant to claims drawn to antisense mediated inhibition of any gene using oligos designed to elicit a reduced immune response, because no antisense-specific gene inhibition has been demonstrated. Furthermore, regarding applicants citation of Agrawal, this statement is considered to support the rejection under enablement, because the rejection clearly stated that one cannot move predictably from *in vitro* results to *in vivo* results. As applicants point out, Agrawal indicates that results *in vivo* are not reflective of those obtained *in vitro*, which supports the stance that one cannot move predictably from *in vitro* results to *in vivo* results, or vice versa.

Applicants also assert that the passages cited from the literature supplied in support of the enablement rejection are not representative of the articles themselves, and are also not reflective of the enablement of the instant invention as claimed. Regarding Braasch, applicants rebut quoted citations of the Office action with a passage citing the advances in the cell biology and clinical trials that afford new options for basic research, biotechnology and medicine. Applicants also cite Braasch in stating that it may be necessary to screen over 20 different oligos to find one

that functions adequately, and argue that when combined with the provided reference of Milner et al., the grounds for enablement of *in vivo* methods has been established.

In response to applicants claims of clinical advances, it is noted that today, there has been only one antisense drug ever approved by the FDA, and even here, it is a drug that is injected directly into the eye, which bypasses cited issues of accessibility and maladaptive immune responses, and is therefore not considered exemplary in any way to treatment methods using oligos that have never been shown to inhibit expression beyond that shown *in vitro*. According to a recent article regarding yet another failed clinical trial involving antisense, Reuter's news service writes that "Isis currently makes the world's only commercial antisense drug -- a treatment for a rare type of eye infection in AIDS patients. Many once-promising antisense drugs have failed, including experimental therapies from Isis for HIV and genital warts." Thus despite applicants citations regarding the promise of the field, such promise has yet to be fulfilled and is not considered to form the basis of enablement of applicants' invention.

Milner et al. does teach a highput screening process as cited by applicant. However, such a method of screening for inhibitors is performed *in vitro*. Since it has been set forth repeatedly that results *in vitro* are not considered predictive of those obtained *in vivo*, the method of Milner is not considered to advance the claim of applicants that screening for *in vivo* inhibitors is routine. Rather, it illustrates the prophetic nature of applicants invention as it pertains to its practice *in vivo* that such a screening process is necessary before one can even consider its use *in vivo*. While applicants statements that the oligos of the instant method are designed to reduce maladaptive immune responses has some merit, there are still several other outstanding issues

that the specification fails to resolve, such as access to the target site, cellular penetration, and non-specific binding of oligos to unintended targets.

Applicants finally argue that the examiner-cited portions of the references of Branch and Tamm both discuss only non-antisense activities of oligonucleotides, while the instant claims are drawn to antisense methods. Applicants argue that it is such problems that the instant claims are designed to deal with, and that these references are therefore not relevant. This is not adopted, because applicants description of their own invention is misleading in this context. The invention is drawn to the use of modified antisense oligos in *in vivo* methods of treatment and target inhibition. As such, the oligos must work *in vivo*. As both Branch and Tamm point out, one of the major issues with the use of antisense oligos *in vivo* is that one cannot predict *a priori* whether an oligo will hybiridize specifically to its target, or alternatively, bind to an unintended target along the way. Both Branch and Tamm indicate that such unintended binding is a significant source of unpredictability when trying to guess whether or not a given oligo will reach its target and inhibit *in vivo*. It is precisely because of such unintended binding that the references of Branch and Tamm were cited, because they describe another set of unresolved issues that lead to the unpredictability cited in the cumulative set of Office actions.

Said claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing any condition or disease suspected of being associated with aberrant gene expression in mammals. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable as described above, one of skill in the art would have been unable to practice the invention without engaging in

undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would thus have been unable to practice the invention over the scope claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz
July 10, 2003